

Anti-CD117 antibody depletes normal and myelodysplastic syndrome human hematopoietic stem cells in xenografted mice.

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Public Summary:

Myelodysplastic syndromes (MDS) are a group of blood disorders in which diseased clones in the bone marrow result in ineffective production of blood. MDS are also associated with an increased risk of transform to acute leukemia. MDS arises from blood forming stem cells; therefore, successful elimination of diseased MDS stem cells is an important part of any curative therapy. However, current treatment options, including allogeneic blood and bone marrow transplantation, often fail to completely eliminate disease-initiating MDS stem cells, and thus have low curative potential and high relapse rates. Here, we demonstrate that human blood stem cells can be safely targeted and eliminated by antibodies that bind a cell-surface molecule present on blood stem cells called CD117 (also known as c-Kit). We show that an anti-human CD117 antibody called SR-1 (originally made in mice), inhibits normal cord blood and bone marrow stem cells in culture. Furthermore, SR-1 and a clinical-grade anti-human CD117 antibody called AMG 191, deplete normal and MDS stem cells in mice engrafted with diseased MDS cells. Anti-CD117 antibodies also permitted the engraftment of normal donor human blood stem cells in engrafted mice with diseased human MDS cells, restoring normal human blood formation and eradicating aggressive pathologic MDS cells. This study is the first to demonstrate that anti-human CD117 antibodies have potential as novel therapeutics to eradicate MDS stem cells and augment the curative effect of allogeneic blood and bone marrow transplantation for this disease. Moreover, we establish the foundation for use of these antibody agents not only in the treatment of MDS but also for the many other blood stem cell-driven and immune disorders for which transplant can be disease-altering.

Scientific Abstract:

The myelodysplastic syndromes (MDS) represent a group of clonal disorders that result in ineffective hematopoiesis and are associated with an increased risk of transformation into acute leukemia. MDS arises from hematopoietic stem cells (HSCs); therefore, successful elimination of MDS HSCs is an important part of any curative therapy. However, current treatment options, including allogeneic hematopoietic cell transplantation (HCT), often fail to ablate disease-initiating MDS HSCs, and thus have low curative potential and high relapse rates. Here, we demonstrate that human HSCs can be targeted and eliminated by monoclonal antibodies (mAbs) that bind cell-surface CD117 (c-Kit). We show that an anti-human CD117 mAb, SR-1, inhibits normal cord blood and bone marrow HSCs in vitro. Furthermore, SR-1 and clinical-grade humanized anti-human CD117 mAb, AMG 191, deplete normal and MDS HSCs in vivo in xenograft mouse models. Anti-CD117 mAbs also facilitate the engraftment of normal donor human HSCs in MDS xenograft mouse models, restoring normal human hematopoiesis and eradicating aggressive pathologic MDS cells. This study is the first to demonstrate that anti-human CD117 mAbs have potential as novel therapeutics to eradicate MDS HSCs and augment the curative effect of allogeneic HCT for this disease. Moreover, we establish the foundation for use of these antibody agents not only in the treatment of MDS but also for the multitude of other HSC-driven blood and immune disorders for which transplant can be disease-altering.

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